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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/863,049	Applicant(s) Lewis
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 4, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 32-39, 43, 50, and 51* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 32-39, 43, 50, and 51* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 13
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response to the Notice to Comply received on 3/4/03 has been entered. This application is now in compliance with the requirements for the disclosure of amino acid and nucleic acid sequences. Applicant's previous response to the restriction/election requirement received on 11/21/02 has also been entered. As requested, claims 9-31, 40-42, and 44-49 have been canceled and new claims 50-51 have been added. Claims 1-8, 32-39, 43, and 50-51 are pending in the instant application. An action on the merits follows.

Restriction/Election

Applicant's election of the subject matter of group I is acknowledged. The applicant has not provided any arguments traversing the grounds for restriction and election of species put forth in the office action mailed to applicants on 9/24/02. Therefore, the restriction requirement is still deemed proper and is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 32-39, 43, and 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting Incontinentia pigmenti (IP) in a human comprising the steps of obtaining a sample from said human and analyzing said sample for an alteration in the nucleic acid sequence of the coding exons of SEQ ID NO:1, wherein said alteration results in inactivation of NF-kB, does not reasonably provide enablement for methods of detecting any NF-kB related medical condition in any organism by analyzing a sample for any alteration in the nucleic acid sequence of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for detecting any NF-kB related medical condition other than for Incontinentia Pigmenti in humans by analyzing a sample for an alteration in the nucleic acid sequence of SEQ ID NO:1. that inactivates NF-kB. At the time of filing, the literature teaches that the NF-kB related medical conditions are primarily derived from mutations which lead to the inappropriate activation of NF-kB rather than the inactivation of NF-kB. Baldwin et al. for instance teaches that the activation of NF-kB may play a role in rheumatoid arthritis, septic shock, Alzheimer's disease, atherosclerosis, and oncogenesis (Baldwin et al., pages 672-674. At the time of filing, the art did not teach diseases or conditions which are related

to the inactivation of NF-kB, although gene knock-out studies did indicate a role for NF-kB in immune responses and hematopoiesis (Baldwin et al., page 661). The specification as written is directed to establishing a link between mutations in NEMO as represented by SEQ ID NO:1 and Incontinentia pigmenti in humans. The specification does not identify or provide any guidance as to other conditions or diseases which are caused by or related to mutations in NEMO or SEQ ID NO:1 which inactivate NF-kB in any organism. Therefore, in the absence of any condition or disease related to NF-kB inactivation known in the art or disclosed by the specification other than Incontinentia pigmenti, the skilled artisan would not have been able to predict without undue experimentation whether the detection of an alteration in NEMO or SEQ ID NO:1 which results in the inactivation of NF-kB would indicate the presence of any disease or condition other than Incontinentia pigmenti.

Furthermore, while the applicants have provided substantial evidence linking deletions and mutations in the coding sequences of the human NEMO gene (SEQ ID NO:1) with Incontinentia pigmenti in human patients with either the familial and sporadic versions of IP, the specification fails to provide sufficient guidance and evidence linking the NEMO genes from other organisms such as mice, cats, birds, and fish with any disease or condition including diseases which resemble IP in humans. In fact, at the time of filing, the striated mouse, which has a mutation in the striated gene not the NEMO gene, was considered a model for IP. The substantial differences between the genetic defects responsible for the IP phenotype in mice versus humans is further demonstrated by the applicants own report that the human homologue of the striated gene responsible for the

phenotype of the striated mouse is not responsible for IP in humans (Aradhya et al. (2000) Am. J. Med. Genet., Vol. 19(3), 241-244). In addition, the specification discloses that knocking-out the murine NEMO gene in mice, while lethal to male offspring, fails to generate females with a phenotype resembling Incontinentia pigmenti in humans (specification, page 58). Prior to the filing of the instant application. Rudolph et al. disclosed that knocking out the NEMO/IKKγ gene in mice results in male embryonic lethality, but that the heterozygous NEMO +/- females appear to be normal (Rudolph et al. (2000) Genes & Devel., Vol. 14, pages 854-862, see page 855). The instant applicants further speculate that the differences in phenotype between NEMO deficient mice and IP patients may be the result of differences in X-inactivation in mice versus humans. Thus, in view of the prior art and evidence of record, the skilled artisan would not have predicted that mutations in a NEMO gene from any organism other than a human would result in an IP like phenotype. It is further noted that the specification and prior art only provide a description of the human and murine NEMO genes. The specification only discloses the sequence of human NEMO, SEQ ID NO:1. The specification fails to provide any description or characteristics of NEMO genes from any other organism such as birds, fish, insects, bacteria, or provide any guidance or evidence that the nucleic acid sequence as set forth in SEQ ID NO:1 is present in any organism other than humans. Therefore, in view of the evidence in the prior art that mutations in the murine form of NEMO do not produce an IP like phenotype, the complete lack of guidance in the specifications regarding the characteristics of NEMO homologues in organisms such as bacteria, insects, fish, or birds, the lack of evidence correlating mutations in NEMO homologues in any

species other than human and any condition or disease, and the breadth of the claims, it would have required undue experimentation to determine whether the detection of alterations in a NEMO gene in a non-human organism would predict, diagnose, or indicate the presence of any disease or condition including Incontinentia pigmenti in the non-human organism. Further, since SEQ ID NO:1 represents the sequence of a human gene, the skilled artisan would not have predicted success in detecting SEQ ID NO:1 in any organism other than a human.

The specification further fails to provide sufficient guidance concerning alterations in any non-coding sequence of SEQ ID NO:1 that result in the inactivation of NF-kB, and that correlate with Incontinentia pigmenti in humans. The specification provides substantial evidence that deletions and point mutations in the coding exons of SEQ ID NO:1 can be correlated with Incontinentia pigmenti in both familial and sporadic cases of IP in human patients. The majority of alterations in SEQ ID NO:1 detected by the applicants are the result of a deletion in the C terminus of the human NEMO. The applicants further report numerous point mutations in various coding exons that also appear to result either a truncated or mutated NEMO gene product that inhibits NF-kB activation. While the specification discloses a number of primer sequences derived from SEQ ID NO:1 for use in detecting mutations in SEQ ID NO:1, only primer pairs which amplify coding exons were able to detect mutations in SEQ ID NO:1 which correlate with loss of NF-kB activity. As noted above, the specification does not provide sequence information for NEMO genes other than human NEMO as set forth in SEQ ID NO:1. The specification also fails to provide any guidance or description of primer pairs or probes useful for amplifying or

hybridizing to coding exons or any other region of any NEMO gene other than human NEMO as set forth in SEQ ID NO:1. Therefore, in view of the lack of guidance provided by the specification for NEMO sequences other than SEQ ID NO:1, and for primer sequences or probes capable of amplifying or hybridizing to NEMO sequences other than SEQ ID NO:1, the evidence of record which demonstrates that mutations which correlate with NF-kB inactivation are located in the coding exons of SEQ ID NO:1, and the breadth of the claims, it would have required undue experimentation at the time of filing for the skilled artisan to detect mutations in NEMO genes in organisms other than humans or to correlate mutations in non-coding regions of SEQ ID NO:1 with inactivation of NF-kB.

Claims 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite methods of detecting an NF-kB related medical condition or Incontinentia pigmenti in an organism by analyzing a sample for an alteration in a NEMO nucleic acid. The specification fails to provide adequate written description for the breadth of NEMO nucleic acids found in all organisms. While the applicant's claims encompass an enormous number of nucleotide sequences, the description present in the instant specification is limited to a description of the human NEMO gene, as set forth in SEQ ID NO:1. The specification fails to provide any description of the nucleic acid sequence or particular physical,

chemical, and biological features of NEMO nucleic acids from any organism other than humans. The Revised Interim Guidelines state " when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus .....In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of NEMO nucleic acids from organisms other than humans, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids or the primers or probes needed for detection of a NEMO nucleic acid in organisms other than humans. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co.*

Ltd., 18 USPQ2d 1016. Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for NEMO nucleic acids other than human NEMO, as set forth in SEQ ID NO:1. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER